REMARKS

Claims 1-114 are pending. Claims 6-10, 19, and 46-114 have been withdrawn from consideration.

Claims 1-5, 11-18, and 20-45 stand rejected.

None of the above changes raise any issue of patentability. Both before and after the above changes, the invention was described in full, clear, concise, and exact terms and met all conditions for patentability under 35 USC 101 *et seq*. The scope of the claims of any resulting patent (and any and all limitations in any of said claims) shall not under any circumstances be limited to their literal terms, but are intended to embrace all equivalents. Accordingly, under no circumstances whatsoever may these claims be interpreted as:

1. having been altered in any way for any reason related to patentability;

2. having been narrowed;

3. a concession that the invention as patented does not reach as far as the original, unamended claim;

4. a surrender of any subject matter as a condition of receiving a patent; and/or,

5. estopping applicants from asserting infringement against every equivalent, whether now known or later developed, foreseen or unforeseen.

Applicants also emphasize that the decision to address the Examiner's suggestions via claim amendment with the understandings set forth above is not in any way intended to avoid the "gatekeeping" role of the PTO with regard to the examination and issuance of valid patents for patentable inventions.

I. INFORMATION DISCLOSURE STATEMENT

The Applicants filed a Supplemental IDS on November 12, 2003. Applicants respectfully request that the Examiner initial and return the Form PTO/SB/08As submitted with Information Disclosure Statement mailed on and November 12, 2003.

II. ELECTION/RESTRICTIONS

The Examiner acknowledges the Applicants' election with traverse of "Group I, claims 1-45 drawn to a pharmaceutical composition comprising at least on insulin secretagogue and at least one FBPase inhibitor herein, and the invention of the species of a particular FBPase inhibitor in the specification and glyburide as insulin secretagogue." (Office Action p. 2) The Examiner goes on to say that upon consideration "the specie election requirement for one FBPase inhibitor herein is modified to include all compounds of Formula 1 and IA, as a single specie." (Office Action p. 2)

The Examiner makes the restriction requirement final and withdraws claims 6-10, 19, and 46-114 from further consideration as being drawn to a non-elected species.

III. 35 U.S.C. § 112 FIRST PARAGRAPH REJECTIONS

The Examiner has rejected claims 1-5, 11-18, and 20-45 as not enabled. The Examiner states:

> while being enabling for the particular compound for driving blood flow to the penis, the particular compounds having the particular formula herein as FBPase inhibitor in combination with glyburide and other particular agents as insulin secretagogue, employed in composition herein, does not reasonably provide enablement for co-administering any compounds represented by a FBPase inhibitor and an insulin secretagogue recited in the claims herein. (Office Action p. 5)

The Examiner cites *In re Wands* and then sets out the factors:

> The nature of the invention: The instant invention pertains to a pharmaceutical composition for treating diabetes in a mammal.
>
> The relative skill of those in the art: The relative skill of those in the art is high.
>
> The breadth of the claims: The instant claims are deemed very broad since the instant claims read on any compounds represented by a FBPase inhibitor and an insulin secretagogue employed in the composition herein.
>
> The amount of direction or guidance presented: Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC 1997) at 1406; stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as

structure as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "it does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art there cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphasis added).

In the instant case, 'represented by a FBPase inhibitor" and "an insulin secretagogue", recited in the instant claims are purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. However, the specification merely provides those particular compounds for each kind of functional compounds for the composition.

Thus Applicants functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (citation omitted)

The predictability or unpredictability: The instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicated that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co*. Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a mammal, the **combination** of any compounds represented by a FBPase inhibitor and an insulin secretagogue,

which may encompass more than a thousand compounds. See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added). In the instant case, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having claimed functional properties in the pharmaceutical compositions herein to be administered to a host. Thus, the teachings of the book clearly support that the instant claimed invention is highly unpredictable.

The presence or absence of working examples and the quantity of experimentation necessary: As discussed above, only those particular compounds for each kind of functional compounds employed in the composition herein is disclosed in the specification. It is noted that only one particular combination of Compound J and glyburide, was tested and is shown in Example X at page 315-316 of the specification. Thus, the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the active agents or compounds in the claimed composition. See MPEP § 716.02(d)

Thus, the specification fails to provide sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds having those functions recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors, the case University of California v. Eli Lilly and Co. (CAFC 1997) and In re Fisher (CCPA 1970) discussed

> above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test all compounds encompassed in the instant claims and their combinations employed in the claimed compositions to be administered to a host, with no assurance of success. (Office Action pp. 5-9)

The Applicants respectfully traverse this rejection.

The Applicants believe that the Examiner did not mean to say that the current claims "while being enabling for the particular compound for driving blood flow to the penis."

The Examiner finds that the functional language occurs at the point of novelty (Office Action p. 7). However, the novelty of the invention is not either an FBPase inhibitor or an insulin secretagogue, but the point of novelty is the combination of these two agents.

The Examiner objects to the use of a functional definition, in spite of case law to the contrary. As stated in MPEP § 2173.05(g), there is nothing inherently wrong with defining some part of an invention through functional terms. In fact the use of functional language has explicitly been approved by the Court of Appeals. When discussing functional language in *Swinehart*, the Court said:

> In our view, there is nothing intrinsically wrong with the use of such a technique in drafting patent claims. Indeed, we have even recognized in the past the practical *necessity* for the use of functional language. *In re Swinehart and Sfiligoj*, 169 U.S.P.Q. 226, 228 (C.C.P.A. 1971).

Furthermore, MPEP § 2173.01 states:

> Applicants may use functional language, alternative expressions, negative limitations, or any style of expression or format of claims which makes clear the boundaries of the subject matter for which the protection is sought. As noted in *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought.

For example, *In re Barr*, the U.S. Court of Customs and Patent Appeals approved the use of functional language in defining the term "incapable of forming a dye with said oxidized developing agent." *See In re Barr*, 170 U.S.P.Q. 330, 337 (C.C.P.A. 1971). The Court went on to say that:

> In summary, we hold that an applicant may invoke the third paragraph of section 112 to justify the specification of one or more elements of a claimed compound in "functional" terms, and that those "functional" terms may be "negative." The real issue in any such case is not whether the

> recital is "functional" or "negative," but whether the recital sets definite boundaries on the patent protection sought - that is, whether those skilled in the relevant art can determine what the claim does or does not read on. Judged by this standard, we think it clear that the controverted language complies with the second paragraph of section 112. *Id.*

Furthermore, a "limited use of terms of effect or result, which accurately define the essential qualities of a product to one skilled in the art, may in some instances be permissible and even desirable." *In re Fuetterer*, 138 USPQ 217, 222 (C.C.P.A. 1963)(quoting *General Electric Co. v. Wabash Appliance Corp.*, 37 USPQ 466, 469 (U.S. 1938)).

The present situation is similar to the *In re Fuetterer* case. In that case, the examiner and the Board rejected certain composition claims as indefinite, ambiguous, unduly broad, and functional, in part because the term "inorganic salts" was defined in a functional way. *Id.* at 218-219. The examiner stated that:

> "Inorganic salt" reads on literally thousands of materials, many of which would *not be operative* for applicant's purpose. For example, some salts *could* readily react with other ingredients in the composition while other salts *could* be corrosive or destructive of the rubber. This recitation is functional since it merely describes how the salt functions as the surface of the tire wears away. *Id.* at 220.

First, the Court found that use of functional language was proper. *Id.* at 222. Then the Court went on to say that the claims were not unduly broad. *Id.* at 223. The Court stated:

> in the words of the *second* paragraph of section 112, "applicant regards as his invention" the combination with his other tread ingredients of *any* inorganic salt *capable* of "maintaining the carbohydrate, the protein, or mixture thereof, in colloidal suspension* * *." It is exactly this combination which appellant has particularly pointed out and *distinctly claimed* in compliance with the *second* paragraph of section 112...Appellant's invention is the *combination* claimed and not the discovery that certain inorganic salts have colloidal suspending properties. We see nothing in the patent law which requires appellant to discover which of all those salts have such properties and which will function in combination. *Id.*

The Court went on to point out that there was no "undue burden" caused by the functional language of the claims:

> The Patent Office would require him to do research on the "literally thousands" of inorganic salts and determine which of these are suitable for incorporation into his claimed combination, apparently forgetting that he has not invented and is not claiming colloidal suspending agents but tire stock composed of a combination of rubber and other ingredients. *Id.*

In addition, numerous other cases have found that the use of functional language is acceptable. *See e.g. In re Herschler*, 200 U.S.P.Q. 711, 717 (C.C.P.A. 1979)(disagreeing with the solicitor who said that a single example of a steroid in the specification could not describe the class of steroids claimed in a functional manner); *In re Edwards*, 196 U.S.P.Q. 465, 467 (C.C.P.A. 1978)(stating that the application is "not intrinsically defective merely because appellants chose to describe their claimed compound by the process of making it); *In re Mattison*, 184 U.S.P.Q. 484, 486 (C.C.P.A. 1975)(saying "General guidelines are disclosed for a proper choice of the substituent Ep together with a representative number of examples."); *Ex parte Schundehutte*, 184 U.S.P.Q. 697 (Bd. Pat. App. & Int. 1974).

In particular, examples of the claimed compounds are often found to be sufficient to guide a person of ordinary skill in the art when it comes to functional claims. For instance, in the *Ex parte Schundehutte* case, the Examiner rejected a claim which read "A reactive dyestuff of the formula...is the radical of an organic dyestuff in which –N-R'$_1$ is bonded directly to an aromatic nuclear carbon atom of F..." *Ex parte Schundehutte*, 184 U.S.P.Q. at 697. The examiner also found the claim was not enabled and lacked written description, because "examples and other exemplary material in the disclosure is not adequately representative of the area covered by the claims and does not provide 'assurance that all of the compounds falling within the scope of the claims will dye fabrics with asserted properties.'" *Id.* at 698. The Board did not agree that the claims were indefinite saying

> While specific methods of use and/or dyeing properties for each and every species covered by the claims have not been demonstrated as pointed out by the examiner, a disclosure of that extent is not required by statute...In the present case, we believe that those skilled in the art could effectively use the reactive dyestuff compounds of the scope covered by the claims, at least without undue experimentation, from the present written description of the invention in the specification, including the numerous examples therein, and from the art recognized properties of dyestuff compounds and conventional methods of using such compounds which those skilled in the dyestuff art are presumed to know. *Id.*

Moreover, the Examiner's legal position that functional language may not be used at the point of novelty is directly contrary to established Federal Circuit law. As the C.C.P.A. said in *In re Swinehart and Sfiligoj*:

> Our study of these cases...satisfies us that any concern over the use of functional language at the so-called 'point of novelty' stems largely from the fear that an applicant will attempt to distinguish over a reference disclosure by emphasizing a property or function which may not be mentioned by the reference and thereby assert that this claimed subject matter is novel. Such a concern is not only irrelevant, it is misplaced...[W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove the subject matter shown to be in the prior art does not possess the characteristics relied on. *In re Swinehart and Sfiligoj*, 169 USPQ 226, 228-29 (C.C.P.A. 1971).

Likewise, in *Ex parte Skinner*, the Board of Patent Appeals and Interferences also acknowledged that a functional limitation may provide novelty to a claim that is otherwise anticipated by a reference. *Ex parte Skinner*, 2 USPQ2d 1788, 1789 (Bd. Pat. App. Int'f 1986). In *Skinner*, the examiner had rejected as anticipated a claim to a mold for making contacting lenses on the basis that the only limitations of the claim not explicitly disclosed by the cited prior art were characteristics of the mold, and that such characteristics may have been inherently present in the prior art mold. *Id.* at 1788. The Board rejected the Examiner's reasoning and explained that the examiner had failed even to make out a *prima facie* case of anticipation:

> We are mindful that there is a line of cases represented by *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971) which indicates that where an examiner has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, the examiner possesses the authority to require an applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on. Nevertheless, before an applicant can be put to this burdensome task, the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art. *Id.* at 1789.

The Board explained that "[a]bsent reasons on the part of the examiner regarding why the natural result of the process used to prepare the mold of [the prior art reference] would have been to achieve the characteristics claimed by appellant's mold, a *prima facie* case of anticipation has not been established." *Id.*

The case law is clear that functional language may provide novelty to a claim that is otherwise anticipated by a prior art reference. *See In re Ludtke*, 441 F.2d 660, 664, 169 USPQ 563 (C.C.P.A. 1971) ("[s]ince the only alleged distinction between claims 1-6 and [the cited reference] is functional language, it was incumbent upon appellants, when challenged, to show that the canopy disclosed by [the reference] does not actually possess such characteristics."); *See also In re Mills*, 916 F.2d 680, 682-83, 16 USPQ2d 1430, 1432-33 (Fed. Cir. 1990) ("*Ludtke* ... dealt with a rejection for lack of novelty, in which case it was proper to require that a prior art reference cited as anticipating a claimed invention be shown to lack the characteristics of the claimed invention .... *That proof would in fact negate the assertion that the claimed invention was described in the prior art.*") (citing *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971) (emphasis added).

The term "M" is defined functionally in claim 11 in that "wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to M-PO_3^{2-}, which inhibits FBPase." In other words, M must be a group that *in vivo* exists as M-PO_3^{2-} and is an inhibitor of FBPase. Additionally, the specification at p. 25, lines 21-28 explains what is meant by an FBPase inhibitor.

> Combinations of the invention include at least one FBPase inhibitor. In most embodiments, the combination will include one FBPase inhibitor. FBPase inhibitors used in the invention are compounds that can inhibit human FBPase activity (Examples A-B), inhibit glucose production from hepatocytes (Examples C-D), lower glucose levels in fasted animals (Examples E-G), or decrease blood glucose levels in diabetic animal models (Examples V and W). Preferred FBPase inhibitors are compounds that inhibit enzyme activity as determined by conducting *in vitro* inhibition studies (Examples A and B).

Like the applicant *In re Fuetterer*, the Applicants are not claiming insulin secretagogues and FBPase inhibitors, but instead a composition containing insulin secretagogues and FBPase inhibitors. Consequently, the Applicants need not list the name or structure of every compound capable of acting as an insulin secretagogue or an FBPase inhibitor.

Furthermore, the Applicants believe that a person of ordinary skill in the art could determine which compounds are FBPase inhibitors through the use of routine experimentation, such as described in Examples A and B. With the use of high-throughput screening, there is nothing undue about the amount of experimentation needed to determine what compounds are encompassed by the claims.

The specification also names several known insulin secretagogues and explains how to determine if other compounds are insulin secretagogues:

> Insulin secretagogues used in this invention typically exhibit activity in assays known to be useful for characterizing compounds that act as insulin secretagogues. The assays include, but are not limited to, those identifying the following exemplified activities: (a) insulin release from pancreatic islets or beta cell lines (Example H), (b) insulin secretion a rat (Example L), (c) glucose lowering in a fasted rat (Example I), (d) intravenous or oral glucose tolerance in a fasted rat (Examples J and K), (e) inhibition of ATP-dependent potassium channels in pancreatic beta cells (Example M), (f) binding to the sulfonylurea receptor (Example N), (g) binding to the GLP-1 receptor, and (h) inhibition of DPP-IV (Example O). Further assays include those described in Bergsten P et al. J. Biol. Chem. 269: 1041-45 (1994); Frodin M et al J. Biol. Chem. 270: 7882-89(1995); Dickinson K et al Eur. J. Pharmacol. 339: 69-76 (1997); Ladriere L et al. Eur. J. Pharmacol. 335: 227-234 (1997); Edwards G, Weston AH Ann. Rev. Pharmacol. Toxicol. 33: 597-637 (1993); Aguilar-Bryan L. et al. Science 268: 423-6 (1995); Thorens B et al. Diabetes 42: 1678-82 (1993); Deacon CF, Hughes TE, Holst JJ Diabetes 47: 764-9 (1998). Especially preferred insulin secretagogues are glyburide, glipizide, and glimepiride, mitiglinide, BTS-67582, repaglinide, and nateglinide. (p. 206, lines 8-23)

The Examiner concludes that the pharmaceutical arts and this invention are unpredictable. (Office Action pp. 7-8) In Example X, the Applicants have shown that the use of this invention results in improved glycemic control. The Applicants are not sure why the Examiner believes that a person of ordinary skill in the art would need to be able to fully predict all possible adverse drug interactions, in order for this invention to be fully enabled. This is not a requirement of section 112.

The Examiner points to Example X as a working example and says that the specification does not provide support for the broad claims. (Office Action pp. 8-9) The Applicants believe that a person of ordinary skill in the art could use the entire scope of the claimed invention without undue

experimentation. As explained above, a person of ordinary skill in the art can easily identify what compounds fall within the scope of the claims.

In view of the above, the Applicants respectfully request that the Examiner withdraw the rejection for lack of enablement.

IV. 35 U.S.C. § 112 SECOND PARAGRAPH REJECTIONS

The Examiner rejects claims 11 and 13 as being indefinite because:

> The expression "M" in claim 11 renders claims 11 and 13 indefinite. The expression "M" is not understood since "M" is not defined in the formula I. Therefore, the scope of the claims is indefinite as to the structural formula encompassed thereby. (Office Action p. 10)

The Applicants respectfully traverse this rejection.

The term "M" is defined functionally in claim 11 in that "wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to M-PO_3^{2-}, which inhibits FBPase." In other words, M must be a group that *in vivo* exists as M-PO_3^{2-} and is an inhibitor of FBPase. As discussed above in Section III, there is nothing inherently wrong with defining a term through its function.

Additionally, the specification at p. 25, lines 21-28 explains what is meant by an FBPase inhibitor.

> Combinations of the invention include at least one FBPase inhibitor. In most embodiments, the combination will include one FBPase inhibitor. FBPase inhibitors used in the invention are compounds that can inhibit human FBPase activity (Examples A-B), inhibit glucose production from hepatocytes (Examples C-D), lower glucose levels in fasted animals (Examples E-G), or decrease blood glucose levels in diabetic animal models (Examples V and W). Preferred FBPase inhibitors are compounds that inhibit enzyme activity as determined by conducting *in vitro* inhibition studies (Examples A and B).

Like the applicant *In re Fuetterer*, the Applicants are not claiming insulin secretagogues and FBPase inhibitors, but instead a composition containing insulin secretagogues and FBPase inhibitors. Consequently, the Applicants need not list the name or structure of every compound capable of acting as an insulin secretagogue or an FBPase inhibitor.

Furthermore, the Applicants believe that a person of ordinary skill in the art could determine which compounds to use through routine experimentation, such as described in Examples A and B. With the use of high-throughput screening, there is nothing undue about the amount of experimentation needed to determine what compounds are encompassed by the claims. A person of ordinary skill in the art could ascertain the metes and bounds of the composition claimed.

In view of the above, the Applicants respectfully request that the Examiner withdraw the indefiniteness rejection.

V. 35 U.S.C. § 103 REJECTIONS

The Examiner has rejected claims 1-5, 11-18, and 20-45 under 103(a) as being unpatentable over Kasibhatla *et al.* and Melchior *et al.* The Examiner states:

> Kasibhatla et al. (WO 98/39342, WO 98/39343, and WO 98/39344) discloses that the instant particular compounds for example having the formula 1 in WO 98/39342, the formula 1 in WO 98/39343, the formula 1 in WO 98/39344, being FBPase inhibitors at the AMP site, are useful in a composition and a method of treating diabetes in a mammal. See WO 98/39342: abstract, page 1 lines 5-10, page 5-15-47 and claims 1-53; WO 98/39344: abstract, page 1, lines 5-10, page 6-36 and all claims therein; WO 98/39343: abstract, page 1 lines 5-10, page 6-75, and all claims therein.
>
> Melchior et al. teaches that the particular insulin secretagogue, sulfonylureas such as glyburide, is well known to be useful in a composition and in the treatment of diabetes in a mammal: See the abstract in particular.
>
> The prior art does not expressly disclose that the employment of the particular FBPase inhibitor of Kasibhatla et al. in combination with that particular insulin secretagogue, sulfonylureas such as glyburide in a composition for the treatment of diabetes.
>
> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular Fbpase inhibitor of Kasibhatla et al. in combination with particular insulin secretagogue, sufonylureas such as glyburide in a composition for the treatment of diabetes.
>
> One having ordinary skill in the art at the time the invention was made would have been motivated to employ the particular Fbpase inhibitor of Kasibhatla et al. in combination with particular insulin secretagogue,

> sufonylureassuch as glyburide in a composition for the treatment of diabetes since both the particular Fbpase inhibitor of Kasibhatla et al., and in particular sufonylureassuch as glyburide are known to be useful in a composition and a method of treating diabetes in a mammal based on the prior art.
>
> Therefore, one of ordinary skill in the art would have reasonably expected that combining the particular Fbpase inhibitor of Kasibhatla et al. in combination with particular insulin secretagogue, sufonylureas such as glyburide both know useful for the same purpose, i.e., treating diabetes, would improve the therapeutic effects for treating the same diseases, and/or would produce additive therapeutic effects in treating the same.
>
> It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.
>
> Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art. (Office Action pp. 10-12)

The Applicants respectfully traverse this rejection.

The current invention is directed toward compositions containing insulin secretagogues and FBPase inhibitors. As the Examiner admits, "the prior art does not expressly disclose that the employment of the particular FBPase inhibitor of Kasibhatla et al. in combination with that particular insulin secretagogue, sulfonylureas such as glyburide in a composition for the treatment of diabetes." (Office Action p. 11)

The Applicants respectfully submit that the Examiner has not presented a *prima facie* case of obviousness. The Examiner bears the initial burden of establishing a *prima facie* case of obviousness, and until such a showing is made, Applicants are under no obligation to present evidence of non-obviousness. *See In re Piasecki*, 223 U.S.P.Q. 785, 787-88 (Fed. Cir. 1984)(acknowledging that the PTO bears the initial burden of establishing a *prima facie* case of obviousness.). To establish a *prima facie* case, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. *See In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art

must have had a reasonable likelihood of success, determined from the vantage point of a skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir 1991). Lastly, the prior art reference or combination or references must teach or suggest all the limitations of the claims. *See In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). It is well established that the teachings or suggestions, as well as the reasonable expectation of success, must come from the prior art, not from the applicant's disclosure. *See In re Vaeck*, 20 U.S.P.Q. 1438, 1442 (Fed. Cir. 1991).

Although improved glycemic control is a reported consequence of treatment with either insulin secretagogues or FBPase inhibitors, the combination of these two drugs is novel. The cited art does not suggest that a combination of insulin secretagogues and FBPase inhibitors will result in any additive effect. A person of ordinary skill in the art would not randomly combine agents that show improved glycemic control and expect that such a combination would be successful.

The following quotation from Example X indicates that improved glycemic control that resulted from combining FBPase inhibitors and insulin secretagogues:

> This study indicates that combination treatment with an insulin secretagogue and an FBPase inhibitor significantly improved glycemic control over treatment with either agent alone. (p. 316, lines 32-34)

The following quotation from the specification also describes the improvements associated with the combination therapy:

> Based on the pharmacological profile of insulin secretagogues and FBPase inhibitors described above, a therapy in which insulin secretagogues are combined with FBPase inhibitors is effective across a broad patient population. In early stage diabetics, FBPase inhibitors and insulin secretagogues are both fully effective. Despite the well-characterized effect of insulin on hepatic glucose output, combination treatment of an insulin secretagogue and an FBPase inhibitor not only provided improved glycemic control in early stage diabetes (Example X), but also reduced the incidence of secondary failure commonly observed with insulin secretagogue monotherapy (Example Y). In advanced diabetics, insulin secretagogues have a high primary failure rate and are only partially effective, whereas the FBPase inhibitors maintain robust efficacy. The benefit of the combination in advanced diabetics is a significant decrease in the number of nonresponders to therapy and an overall increased degree of glycemic control. While the initial response of combination therapy in advanced diabetics may in large part be due to treatment with the FBPase

> inhibitor, blood glucose lowering improves pancreatic function and allows the insulin secretagogue to become more fully effective over time and in the long term thus provides improved response to the insulin secretagogue and enhanced glycemic control. (p. 207, line 18 – p. 208, line 3)

The glycemic control that resulted from the combination of this invention was significantly greater than that obtained by administration of either agent alone. (*see* Figure 1 p. 317) Although, a person of ordinary skill in the art might have expected that the combination of insulin secretagogues or FBPase inhibitors would result in glycemic control, they would not have known that the combination of this invention would result in significantly greater glycemic control than that obtained by administration of either agent alone.

In view of the above, the Applicants respectfully request that the Examiner withdraw the obviousness rejection.

VI. DOUBLE PATENTING REJECTIONS

The Examiner provisionally rejects claims 1-5, 11-18, and 20-45 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over all the claims of copending Application No. 09/470649. The Examiner says:

> The claim of the instant application is drawn to employ the same Fbpase inhibitor in combination with insulin secretagogue, such as sulfonylureas, e.g., gylburide in a composition for the treatment of diabetes. Thus, the two compositions in the copending Application and the instant Application are seen to substantially overlap. (Office Action p. 13)

The Applicants respectfully traverse this rejection.

The Applicants note that Application No. 09/470649 has been allowed and is now U.S. Patent No. 6,756,360. Since the Examiner has not had an opportunity to review the issued claims and an obviousness-type double patenting rejection is based on a comparison of the claims of the issued patent to the pending claims, the Applicants respectfully request removal of the provisional rejection and ask the Examiner to reevaluate her rejection based on the issued claims.

The Applicants do wish to point out that a person of ordinary skill in the art would not reasonably expect that the successful combination of one agent useful in the treatment of diabetes with an FBPase inhibitor would mean that combining another agent useful in treating diabetes with an

FBPase inhibitor would be successful, particularly when the agents useful in treating diabetes operate by different mechanisms.

Isulin secretagogues and insulin sensitizers operate by different mechanisms as noted in the specification of the current Application:

> The **insulin secretagogues** target defects in insulin secretion by the pancreas, defects which are typically observed in diabetics. (p. 2, lines 18-20)(emphasis added)
>
> **Insulin sensitizers** are another class of oral agents. Peroxisome proliferator-activated receptors (PPAR-gammas) appear to be the target of the most recently introduced class of antidiabetic agents, the insulin sensitizers. These drugs are reported to enhance insulin-mediated glucose disposal and inhibition of hepatic glucose output without directly stimulating insulin secretion. (p. 2 line 30 – p. 3, line 3)(emphasis added)

The Applicants also respectfully ask the Examiner to contact the undersigned if she wishes to maintain this rejection.

CONCLUSION

In view of the above remarks, it is believed that the application is in condition for allowance, and such action is respectfully requested at the Examiner's earliest convenience.

Respectfully Submitted,

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